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Increased Body Mass Index Is a Risk Factor for Poor Clinical Outcomes after Radical Prostatectomy in Men with International Society of Urological Pathology Grade Group 1 Prostate Cancer Diagnosed with Systematic Biopsies

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Keywords
Prostate cancer · Body mass index · Obesity · International Society of Urological Pathology

Abstract
Introduction: The association between obesity and clinically significant prostate cancer (PCa) is still a matter of debate. In this study, we evaluated the effect of body mass index (BMI) on the prediction of pathological unfavorable disease (UD), positive surgical margins (PSMs), and biochemical recurrence (BCR) in patients with clinically localized (≤cT2c) International Society of Urological Pathology (ISUP) grade group 1 PCa at biopsy. ***Methods:*** 427 patients with ISUP grade group 1 PCa who have undergone radical prostatectomy and BMI evaluation were included. The outcome of interest was the presence of UD (defined as ISUP grade group ≥3 and pT ≥3a), PSM, and BCR. ***Results:*** Statistically significant differences resulted in comparing BMI with prostate-specific antigen (PSA) and serum testosterone levels (both $p < 0.0001$). Patients with UD and PSM had higher BMI values ($p < 0.0001$ and $p = 0.006$, respectively). BCR-free survival was signifi-

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cantly decreased in patients with higher BMI values ($p < 0.0001$). BMI was an independent risk factor for BCR and PSM. Receiver-operating characteristic analysis testing PSA accuracy in different BMI groups, showed that PSA had a reduced predictive value (area under the curve [AUC] = 0.535; 95% confidence interval [CI] = 0.422–0.646), in obese men compared to overweight (AUC = 0.664; 95% CI = 0.598–0.725) and normal weight patients (AUC = 0.721; 95% CI = 0.660–0.777). ***Conclusion:*** Our findings show that increased BMI is a significant predictor of UD and PSM at RP in patients with preoperative low-to intermediate-risk diseases, suggesting that BMI evaluation may be useful in a clinical setting to identify patients with favorable preoperative disease characteristics harboring high-risk PCa.

Introduction

More than 20 years ago, the World Health Organization identified obesity as a global health problem that has grown to epidemic proportions [1]. Many studies have demonstrated the negative impact of the excessive accumulation of body fat and various diseases and clinical conditions such as metabolic syndrome, type 2 diabetes, cardiovascular disease, obstructive sleep apnea, osteoarthritis, and liver disease [2–4]. Moreover, obesity has also been associated with increased risks of a number of cancers, including endometrial cancer, gastrointestinal cancers, meningioma, multiple myeloma, and urological tumors [5–9].

About prostate cancer (PCa), several mechanisms have been proposed to explain the association between obesity and its increased incidence and the risk of biochemical recurrence (BCR) after radical prostatectomy [10–12]. An opening question remains the understanding of mechanisms that regulate the prostate-specific antigen (PSA) levels and the biological aggressiveness of PCa in obese men. In addition, delayed diagnosis of PCa represents another critical issue in men with increased body mass index (BMI). The diagnostic delay may be caused by a variety of factors, including lower PSA values as an effect of hemodilution and lower levels of testosterone, as well as a consequence of a low diagnostic accuracy of prostate biopsies in larger prostate [13, 14].

A delayed diagnosis of PCa in men with increased BMI might translate to a worse prognosis and might in part explain the high rate of capsular incision and positive surgical margin (PSM) at the time of radical prostatectomy, as well as an increased risk of BCR after surgery [15, 16]. In this study, we evaluated the effect of BMI on the prediction of pathological unfavorable disease (UD), PSMs, and BCR in patients with clinically localized (≤cT2c) International Society of Urological Pathology (ISUP) grade group 1 PCa at biopsy.

Materials and Methods

Patients

This study included 427 consecutive men with localized ISUP grade 1 PCa, who underwent laparoscopic or robot-assisted RP within 3 months from diagnosis, between January 2009 and December 2015. RP specimens were processed and evaluated according to the Stanford protocol [9] by 2-experienced genitourinary pathologists, blinded to the test results of each institution.

For all patients, biopsies were analyzed according to the 2014 ISUP recommendations [17, 18]. Prostate biopsies were performed using a transrectal approach. During the procedure, an experienced urologist measured the prostate volume and carried out 12–18 core biopsies using an 18-G Tru-Cut needle.

None of the study patients received neoadjuvant hormonal therapy (antiandrogens or luteinizing hormone-releasing hormone analogs or antagonists) or other hormonal preparations (i.e., 5-α reductase inhibitors) that could alter their PSA values. We also excluded patients with acute bacterial prostatitis or previous prostate surgery in the 3 months before biopsy. In addition, subjects with chronic renal disease, alterations in blood protein levels at electrophoresis, hemophilia, incurable endocrine diseases, or those who had previously undergone multiple transfusions were excluded from the study because these conditions could alter the concentration of total PSA and testosterone. All patients underwent systematic blood sampling between 7:00 and 10:00 a.m. on the day before surgery to assess serum total testosterone concentrations.

Data collected included age, preoperative PSA level, PSA density, pathological stage, serum total testosterone, and BMI. For low-risk localized PCa, no additional imaging was recommended for staging purposes according to EAU guidelines [19].

The patients were stratified according to ISUP grade groups 1–5. BMI groups were defined by the WHO as follows: normal weight (18.5–24.9 kg/m^2, $n = 225$), overweight (25–29.9 kg/m^2, $n = 95$), and obese (>30 kg/m^2, $n = 82$). Disease upstaging was regarded as pathological stage ≥T3a after RP with clinical stage ≤T2c. PCa upgrading was defined as ISUP grade group ≥3 in RP specimens. UD was defined as the occurrence of pathological stage ≥pT3 and ISUP grade group ≥3 at RP specimens' pathology. BCR following RP was defined according to EAU guidelines.

The protocol for the research project has been approved by the local hospital Ethics Committees and conforms to the provisions of the 1995 Declaration of Helsinki. Written informed consent was obtained from all patients.

Statistical Analysis

Statistical calculations were performed with MedCalc 9.2.0.1 (MedCalc Software, Mariakerke, Belgium) and PASW 18 software (PASW 18; SPSS, Chicago, IL, USA). Comparisons of median values of the various variables between different groups were evaluated by Mann-Whitney U test or Kruskal-Wallis as appropriate.

Table 1. Clinical and pathological characteristics by BMI

Variable	BMI group		
	normal BMI <25 kg/m^2	overweight BMI 25–29.9 kg/m^2	obese BMI >30 kg/m^2
Patients, *n*	225	95	82
Age at diagnosis, median (95% CI)	64 (63–65)	66 (65–67.5)	63 (60–66)
PSA, ng/mL at diagnosis, median (95% CI)	5.86 (5.36–6.11)	5.2 (4.93–5.76)	4.25 (4.00–5.09)
Prostate volume, mL, median (95% CI)	49 (45–50)	45 (44–49)	49 (45–52)
PSA density, median (95% CI)	0.12 (0.11–0.12)	0.12 (0.11–0.13)	0.14 (0.12–0.14)
Testosterone, median (95% CI)	500 (456–532)	400 (300–501)	288 (271–390)
Nr of cores, median (95% CI)	12 (12–12)	14 (14–14)	14 (12–14)
Nr of positive cores, 2; *n* (%)	92 (40.8)	51 (53.6)	46 (56.1)
Max % of core involved by tumor, median (95% CI)	20 (20–25)	20 (20–30)	35 (30–40)
Pathological stage, *n* (%)			
pT2	211 (93.7)	90 (94.7)	58 (70.7)
pT3	14 (6.3)	5 (5.3)	24 (29.3)
ISUP, *n* (%)			
1	177 (78.6)	43 (45.3)	19 (23.2)
2	24 (10.7)	24 (25.3)	18 (21.9)
3	22 (9.8)	26 (27.3)	31 (37.8)
4	2 (0.9)	2 (2.1)	4 (4.9)
5	0	0	10 (12.2)

BMI, body mass index; CI, confidence interval; ISUP, International Society of Urological Pathology.

The predictive accuracy of PSA and BMI for BCR was evaluated using receiver-operating characteristic (ROC) analysis and quantified in terms of area under the curve (AUC) and corresponding 95% confidence interval (95% CI). Stepwise logistic regression was performed to determine factors influencing PSM.

Univariate and Multivariate analyses were performed using the Cox proportional hazards regression model to identify the most significant variables for predicting BCR. A backward selection procedure was performed with removal criterion $p > 0.10$ based on likelihood ratio tests. Model calibration was measured by the Hosmer-Lemeshow goodness of fit test, with $p < 0.05$ considered statistically significant.

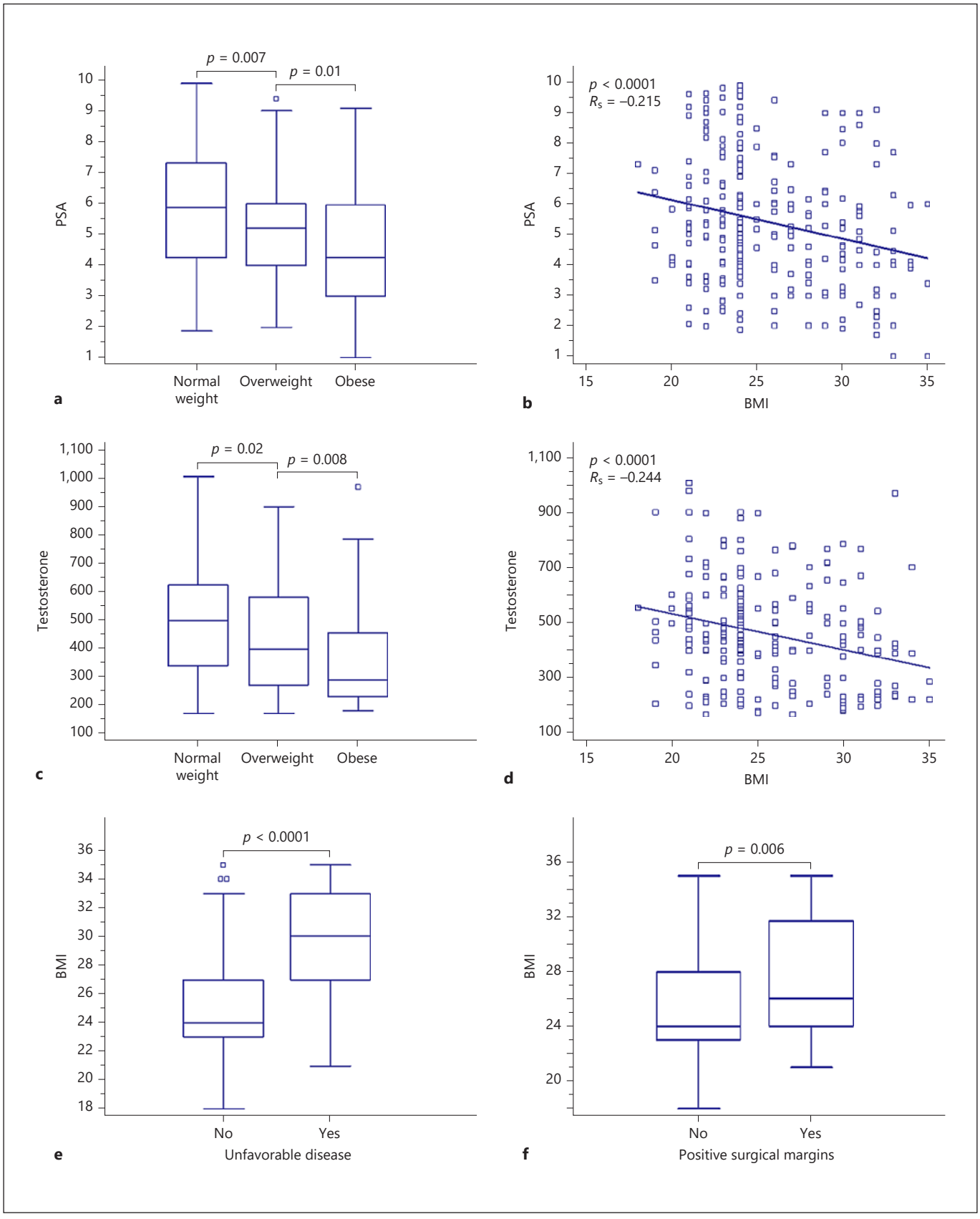
Spearman test was applied to evaluate the correlations between BMI values, PSA, and testosterone. A p value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the overall study population are summarized in Table 1. PSA values and testosterone levels were lower in those patients classified as overweight or obese. An inverse correlation has been shown between PSA and BMI values (Spearman correlation: $r_s = -0.215$, $p < 0.0001$). Similarly, an inverse correlation has been observed between total testosterone levels and BMI ($r_s = -0.244$, $p < 0.0001$). In addition, patients with UD and PSMs had higher BMI values ($p < 0.0001$ and $p = 0.006$, respectively) (Fig. 1a–f).

Kaplan-Meier survival curves for BCR-free survival, stratified by BMI groups, are shown in Figure 2. BCR-free survival was significantly decreased in patients with BMI >30 kg/m^2 ($p < 0.0001$). Logistic regression model showed that increased BMI and higher percentage of positive cores in biopsy specimens were risk factors for PSM (Table 2).

Multivariate analysis including age, BMI, PSA, PSM, and ISUP grade groups as covariates (Table 3) showed that BMI and PSA were significant independent predictors of BCR, with the Hosmer-Lemeshow statistics showing adequate model calibration ($p = 0.24$). ROC analysis testing the performance of PSA and BMI in predicting BCR showed that BMI had the highest AUC compared to PSA (AUC = 0.792 [95% confidence interval (CI) = 0.750–0.829] vs. AUC = 0.589 [95% CI = 0.541–0.636], respectively. $p < 0.001$). In addition, ROC analysis testing PSA accuracy in different BMI groups, showed that PSA had a reduced predictive value (AUC = 0.535; 95% CI = 0.422–0.646) in obese men compared to overweight (AUC = 0.664; 95% CI = 0.598–0.725) and normal weight patients (AUC = 0.721; 95% CI = 0.660–0.777).



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Discussion

Altered adipose tissue homeostasis may be an important contributor to the development and/or progression of a number of solid organ tumors, including PCa [10–12]. Recent evidence supports a positive association between obesity and increased risk of cancer, with stronger links to more aggressive disease [20–22]. Increased adiposity can sustain tumorigenesis by providing critical metabolites for cancer growth and pro-inflammatory cytokines, which are major drivers for many types of tumors, including PCa [23–25]. It has been shown that high BMI men have lower testosterone levels, which predispose them to more aggressive disease and poor prognosis PCa [13, 14], and indeed, in our study, statistically significant differences resulted between BMI groups, total serum testosterone, PSM, and UD.

Furthermore, increasing evidences suggested that obesity, measured by BMI, is associated with increased risk of PCa-specific mortality and BCR [26–28]. In our cohort, BMI and PSA were significant independent predictors of BCR, and according to the Kaplan-Meier survival curves stratified by BMI groups, BCR-free survival was significantly decreased in patients with BMI >30 kg/m^2.

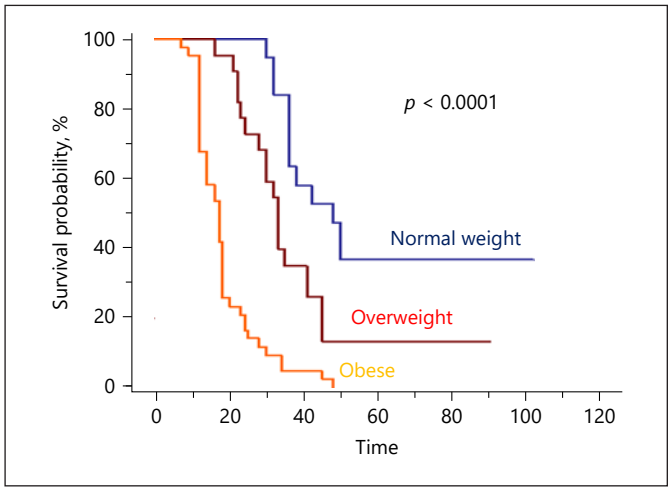

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Fig. 2. Kaplan-Meier curves for BCR-free survival stratified by BMI groups. BMI, body mass index; BCR, biochemical recurrence.

In addition, in our study, we found an increased rate of a pT3 disease (29.3%) in obese men compared to normal or overweight patients (5–6%). Several studies showed more adverse pathological features in obese men undergoing radical prostatectomy, and it is evident that obesity makes early detection of PCa more difficult due to less PSA screening, lower accuracy of digital rectal examination in obese men, and lower PSA values caused by obesity-related hemodilution [29, 30]. As shown in the ROC analysis testing PSA accuracy in different BMI groups, PSA had a reduced predictive value in obese men compared to overweight and normal weight patients.

Nowadays, there is an attitude to extend active surveillance protocols not only to GG1 but also to GG2 disease with one high-grade core at the biopsy [31]; nevertheless, we have to be careful in the decision-making. In this scenario, recent studies showed that obesity is independently associated with a higher risk of pathological and therapeutic progression after initial biopsy [32], and data from another study support the idea that obesity is associated with PCa aggressiveness with a higher risk of upgraded and upstaged disease [33]. Therefore, active surveillance protocols in this subset of patients should include close surveillance scheme in order to early identify tumor progression.

Positive surgical margins play a key role in predicting clinical outcomes after RP. Yu et al. [34] demonstrated that obese patients showed a significant association with adverse surgical outcomes such as PSM, and according to the results of our survival analyses, it could be postulated that obesity-associated pathological variables simultaneously influenced BCR-free survival. Furthermore, obese patients had greater PSM and were statistically significant predictors of BCR-free survival after RP.

Current data would suggest that although BMI is a valid parameter, other criteria should be considered to stratify obese patients and their prognosis after RP. Adipose tissue and, in particular, the perivisceral fat, is metabolically active and has a particular inflammatory profile [35]. Recent studies have demonstrated that an increased thickness of the adipose tissue surrounding the neoplastic prostate (periprostatic adipose tissue [PPAT]) was associated with poor clinical outcomes and the presence of high-grade disease [36–39].

Fig. 1. a PSA levels stratified according to BMI groups. **b** Scatter diagram with regression line between BMI and PSA values. **c** Testosterone levels stratified according to BMI groups. **d** Scatter diagram with regression line between BMI and testosterone values. **e** Distribution of BMI according to the presence of UD. **f** Distribution of BMI according to the presence of PSMs. PSA, prostate-specific antigen; BMI, body mass index; UD, unfavorable disease; PSM, positive surgical margin.

Table 2. Logistic regression model for PSMs

Variable	OR	95% CI	*p* value
BMI	1.95	1.15–3.28	0.01
Percentage of positive cores in biopsy specimens	1.81	1.16–3.02	0.01
PSA at diagnosis	1.02	0.92–1.15	0.68
Prostate volume	0.95	0.91–1.01	0.21

BMI, body mass index; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen; PSM, positive surgical margin.

Table 3. Cox proportional hazards regression model for BCR prediction

Variable	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.04 (1.01–1.12)	0.01		–
ISUP group	2.53 (1.72–3.96)	0.01		–
BMI	1.18 (1.09–1.42)	0.0001	1.23 (1.14–1.32)	0.001
PSA	1.09 (1.02–1.12)	0.0001	1.16 (1.04–1.31)	0.008
PSM	2.21 (2.04–3.28)	0.01		–

BMI, body mass index; CI, confidence interval; PSA, prostate-specific antigen; PSM, positive surgical margins; ISUP, International Society of Urological Pathology; BCR, biochemical recurrence.

Salji et al. [40] first observed, by accurately quantifying the volume of PPAT by MRI, that PPAT volume measurement is a better prognostic tool for identifying patients at risk of developing castration-resistant PCa. The results from Sasaki et al. [41] showed that pretreatment ratio of PPAT to subcutaneous fat thickness on MRI is an independent survival predictor in hormone-naive men with advanced PCa. Interestingly, PPAT but not visceral fat was associated with OS in patients with advanced PCa at the time of diagnosis, opening to the future prospective that is moving along to evaluate patient's PPF thickness as a better prognostic tool [41].

The present study had some limitations. First, there might have been the inherent bias of a retrospective design and a selection bias. The data were analyzed in selected patients who underwent RP rather than all patients with biopsy-confirmed PCa. In addition, we used only BMI as a clinical parameter in order to evaluate overweight/obesity. In a recent article, Shachar et al. suggested to evaluate body composition beyond BMI and to use different parameters for a better risk stratification [42].

Conclusions

Our findings suggest that in patients with preoperative low-to intermediate-risk disease, an increased BMI is a predictor of unfavorable prognosis according to the most recently proposed PCa grading system. Therefore, BMI evaluation may be useful in a clinical setting to identify patients with favorable preoperative disease characteristics harboring high-risk PCa.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol for the research project has been approved by the local hospital Ethics Committees. Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

(1) Conception and design: F.M. and L.G.; (2) administrative support: F.M. and M.M.; (3) provision of study materials or patients: all the authors; (4) collection and assembly of data: F.M.; (5) data analysis and interpretation: L.G. and F.M.; (6) manuscript writing: all the authors; (7) final approval of manuscript: all the authors.

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